

STATE-OF-THE-ART PAPER

Safety and Efficacy of Antiplatelet and Antithrombotic Therapy in Acute Coronary Syndrome Patients With Chronic Kidney Disease

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Chronic kidney disease (CKD) is prevalent and affects an ever-increasing proportion of patients presenting with acute coronary syndrome (ACS). Patients with CKD have a higher risk of ACS and significantly higher mortality, and are also predisposed to increased bleeding complications. Antiplatelet and antithrombotic drugs form the bedrock of management of patients with ACS. Most randomized trials of these drugs exclude patients with CKD, and current guidelines for management of these patients are largely based on these trials. We aim to review the safety and efficacy of these drugs in patients with CKD presenting with ACS. (J Am Coll Cardiol 2011;58:2263–9)

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Chronic kidney disease (CKD) as defined by the National Kidney Foundation includes a mild reduction of glomerular filtration rate (GFR) in the presence of kidney damage (stage 2), and moderate to severe reductions in GFR even in the absence of kidney damage (stages 3 to 5) (Table 1). The National Kidney Foundation estimates that 11% of the U.S. population has CKD (1). Data from clinical trials suggest that 35% to 40% of patients presenting with an acute coronary syndrome (ACS) have some degree of renal insufficiency (2,3). Chronic kidney disease is an independent predictor of outcome in patients presenting with ACS. Cardiovascular disease is the leading cause of death in patients with CKD (1,4).

Patients with renal insufficiency are known to have a graded increased risk for thrombosis (5) and bleeding (6,7). Uremia is associated with prolongation of bleeding time and abnormal platelet aggregation and adhesion due to intrinsic and extrinsic factors (Fig. 1) (8). The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for management of ACS clearly acknowledge the lack of sufficient studies so as to make specific recommendations for patients with CKD (9). A recent study showed that patients with CKD were excluded from 75% of published coronary artery disease trials (10). It is extremely important for practitioners to become familiar with the sites of action of all the antiplatelet and antithrom-

botic drugs, as shown in Figure 2, to make judicial decisions regarding CKD patients. Table 2 also shows the recommended dose, half-life, route of elimination, and dose adjustment of most approved anticoagulants, as well as potential methods to reverse bleeding for each of these agents.

Antiplatelet and Antithrombotic Drugs

The antiplatelet and antithrombotic drugs used for treating patients with CKD are shown in Table 3.

Aspirin. The efficacy of aspirin for patients with CKD presenting with ACS is well established. In the Cooperative Cardiovascular Project (11), McCullough et al. (12) showed that aspirin reduced in-hospital mortality by 64.3% to 80% across all quartiles of creatinine clearance (CrCl). In addition, patients who were not receiving aspirin on admission were more likely to be in heart failure or cardiogenic shock. A recent retrospective review of 595 patients with ACS found that the use of aspirin was associated with a decreased rate of ST-segment elevation myocardial infarction in patients with GFR <60 ml/min (odds ratio [OR]: 0.5, 95% confidence interval [CI]: 0.2 to 1.0; $p = 0.05$) (13). Data from the National Cardiovascular Data ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry, including 19,029 patients with ST-segment elevation myocardial infarction and 30,462 with non-ST-segment elevation myocardial infarction, documented decreasing use of aspirin with worsening severity of CKD (14,15). The U.K. HARP (Heart and Renal Protection)-1 trial and the DOPPS (Dialysis Outcomes and Prescription Patterns Study) showed that low-dose aspirin (100 mg/day) in CKD patients was not associated with increased major

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Manuscript received February 11, 2011; revised manuscript received August 12, 2011, accepted August 21, 2011.

Abbreviations and Acronyms

ACC	= American College of Cardiology
ACS	= acute coronary syndrome(s)
AHA	= American Heart Association
AMI	= acute myocardial infarction
CI	= confidence interval
CKD	= chronic kidney disease
CrCl	= creatinine clearance
GFR	= glomerular filtration rate
GPI	= glycoprotein IIb/IIIa inhibitor
OR	= odds ratio

bleeding or progression of CKD (16,17). In a recent meta-analysis by the Antithrombotic Trialists Collaboration, low-dose aspirin (75 to 160 mg) was found to be as efficacious as high-dose aspirin (325 mg) beyond the acute phase for secondary prevention of coronary artery disease in patients with CKD and end-stage renal disease (18).

Clopidogrel. The current ACC/AHA guidelines recommend the use of clopidogrel in patients with ACS (9,19). No specific recommendations exist for the adjustment of clopidogrel dosage in renal insufficiency. A post-hoc analysis from the CREDO (Clopidogrel for Reduction in Events During Observation) trial, patients with

mild and moderate CKD did not have any significant difference in outcomes (mild 10.3 % vs. 12.8%, $p = 0.30$; moderate 17.8% vs. 13.1%, $p = 0.24$) with increased risk of bleeding with clopidogrel (20).

A post-hoc analysis of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial (21–23) showed no interaction between clopidogrel and renal function (p value for homogeneity 0.11). However, there was no significant benefit from using clopidogrel for patients in the lowest tertile (relative risk: 0.89 [95% confidence interval [CI]: 0.76 to 1.05]), and patients in this group had a significant increase in minor bleeding (hazard ratio: 1.5, 95% CI: 1.21 to 1.86) and blood transfusion (3.5%).

Deray et al. (24), compared platelet inhibition using 75 mg of clopidogrel in patients with moderate and severe CKD, and demonstrated similar clopidogrel-induced platelet inhibition in both groups. Park et al. (25) compared clopidogrel responsiveness in normal persons ($n = 23$) and patients with CKD treated with 75 mg ($n = 18$) and 150 mg ($n = 18$) of clopidogrel. They found decreased platelet inhibition in patients with CKD even with doubling the dose of clopidogrel (25). A recent study by Cuisset et al. (26) evaluated the effect of CKD on platelet aggregation in patients with ACS given clopidogrel (600 mg loading dose followed by 150 mg daily). There was no difference in platelet aggregation acutely and at 30 days. Clinical effect of CKD in patients administered double-dose clopidogrel in the OASIS-7 (Seventh Organization to Assess Strategies in Acute Coronary Syndrome) trial is not available.

Prasugrel. Prasugrel is a third-generation thienopyridine (27–29). Small et al. (30) conducted a study comparing the pharmacokinetics and pharmacodynamics of prasugrel in patients with normal renal function, moderate renal insufficiency, and end-stage renal disease. The levels of the active metabolite of prasugrel were not affected by moderate renal

impairment, but decreased by 40% in end-stage renal disease, although with similar platelet inhibition levels. Inhibition of platelet aggregation was similar in all groups (30). So far, there are no studies on clinical outcomes with prasugrel in patients with CKD.

Ticagrelor. Ticagrelor is a more potent inhibitor of platelet aggregation (31,32). A subanalysis of the PLATO (Ticagrelor versus Clopidogrel in Patients in Acute Coronary Syndrome) trial showed CKD patients ($GFR < 60$ ml; $n = 3,237$) have a greater reduction in events (17.3% vs. 22%; hazard ratio: 0.77 [95% CI: 0.65 to 0.90]) and mortality (10% vs. 14%; hazard ratio: 0.72 [95% CI: 0.58 to 0.89]) as compared to non-CKD: 4.7% per year vs. 1% per year, respectively (34). Ticagrelor offers an alternative option for treating ACS patients with CKD.

Glycoprotein IIb/IIIa inhibitors. Intravenous glycoprotein IIb/IIIa inhibitors (GPIs) block the final pathway for platelet aggregation (34,35). Frilling et al. (36) compared the efficacy of abciximab in normal and CKD patients. Patients in either group had similar clinical outcomes. The CKD patients had more episodes of major bleeding (4.5% vs. 0.6%; $p = 0.003$) but similar episodes of minor bleeding and thrombocytopenia. Similar findings were reported by the Mayo Clinic (37). A recent study by Pinkau et al. (38) evaluated adding abciximab to aspirin and clopidogrel in CKD patients undergoing PCI. There was no significant interaction between abciximab, renal function, and bleeding complications ($p = 0.22$). Alam et al. (38) showed that patients with $CrCl < 60$ ml/min have $< 10\%$ platelet aggregation at 25 ng/ml tirofiban, one-third the standard effective dose in non-CKD patients.

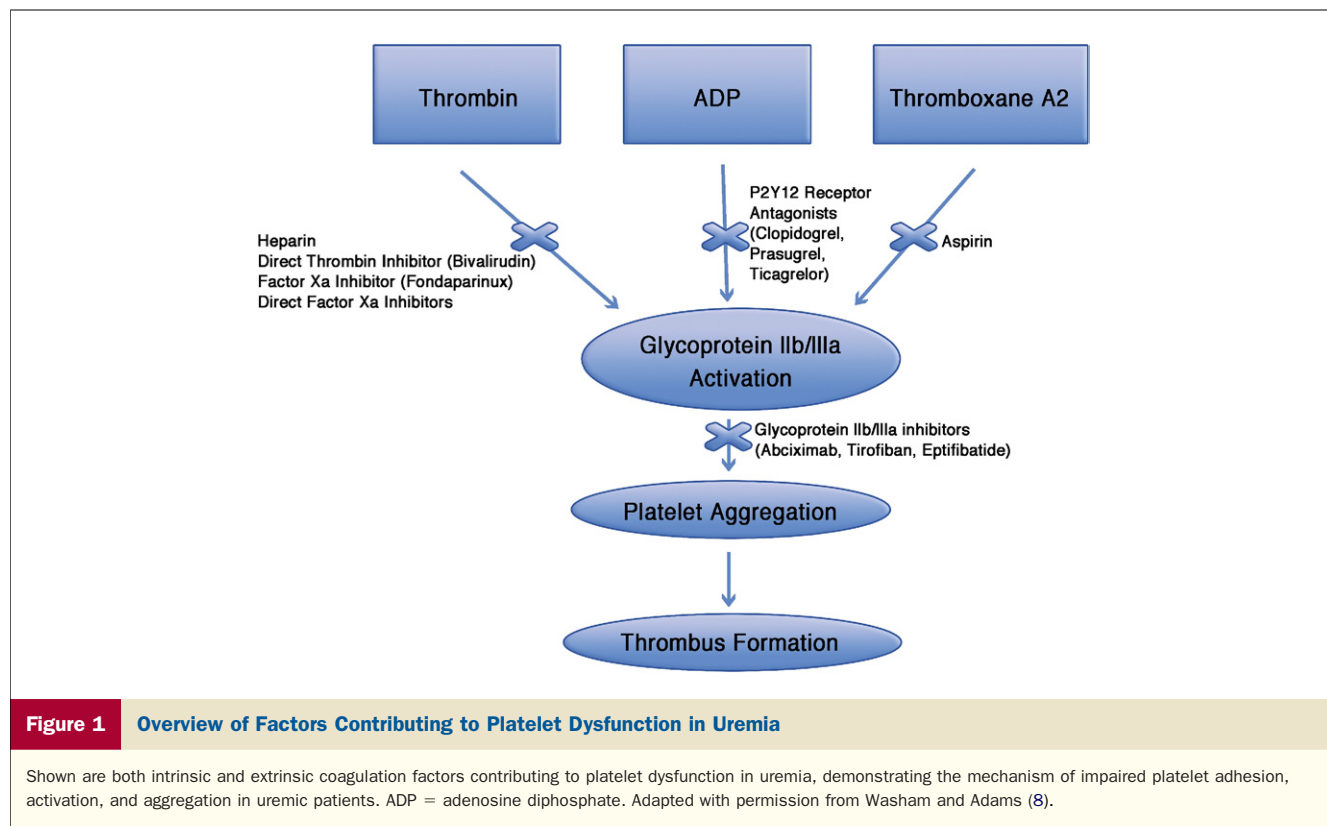
A subgroup analysis of the PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) trial showed that TIMI (Thrombolysis In Myocardial Infarction) major bleeding was not significantly worsened by renal dysfunction or the use of tirofiban ($p = 0.35$ and $p = 0.20$, respectively). However, the combined endpoint of TIMI major and minor bleeding was increased with worsening renal function ($p = 0.004$) as well as use of tirofiban ($p = 0.04$).

A subanalysis of the TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Outcome) trial (40) based on creatinine clearance (< 70 , 70 to 90, 90 to 114, and > 114 ml/min) showed that patients with lower $CrCl$ have higher ischemic and bleeding events. The ESPRIT (Enhanced

Table 1 National Kidney Foundation Classification of CKD Based on GFR

Classification	Definition
Normal	$GFR > 90$ ml/min/ 1.73 m ² with no evidence of kidney dysfunction
CKD 1	$GFR > 90$ ml/min/ 1.73 m ² with evidence of kidney dysfunction
CKD 2	GFR 60–90 ml/min/ 1.73 m ²
CKD 3	GFR 30–60 ml/min/ 1.73 m ²
CKD 4	GFR 15–30 ml/min/ 1.73 m ²
CKD 5	$GFR < 15$ ml/min/ 1.73 m ²

CKD = chronic kidney disease; GFR = glomerular filtration rate.



Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy) trial (41–43) showed that treatment benefit with eptifibatide was seen irrespective of renal function, and

it was greater in patients with mild renal insufficiency. Data from the PROTECT trial (44) and the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients

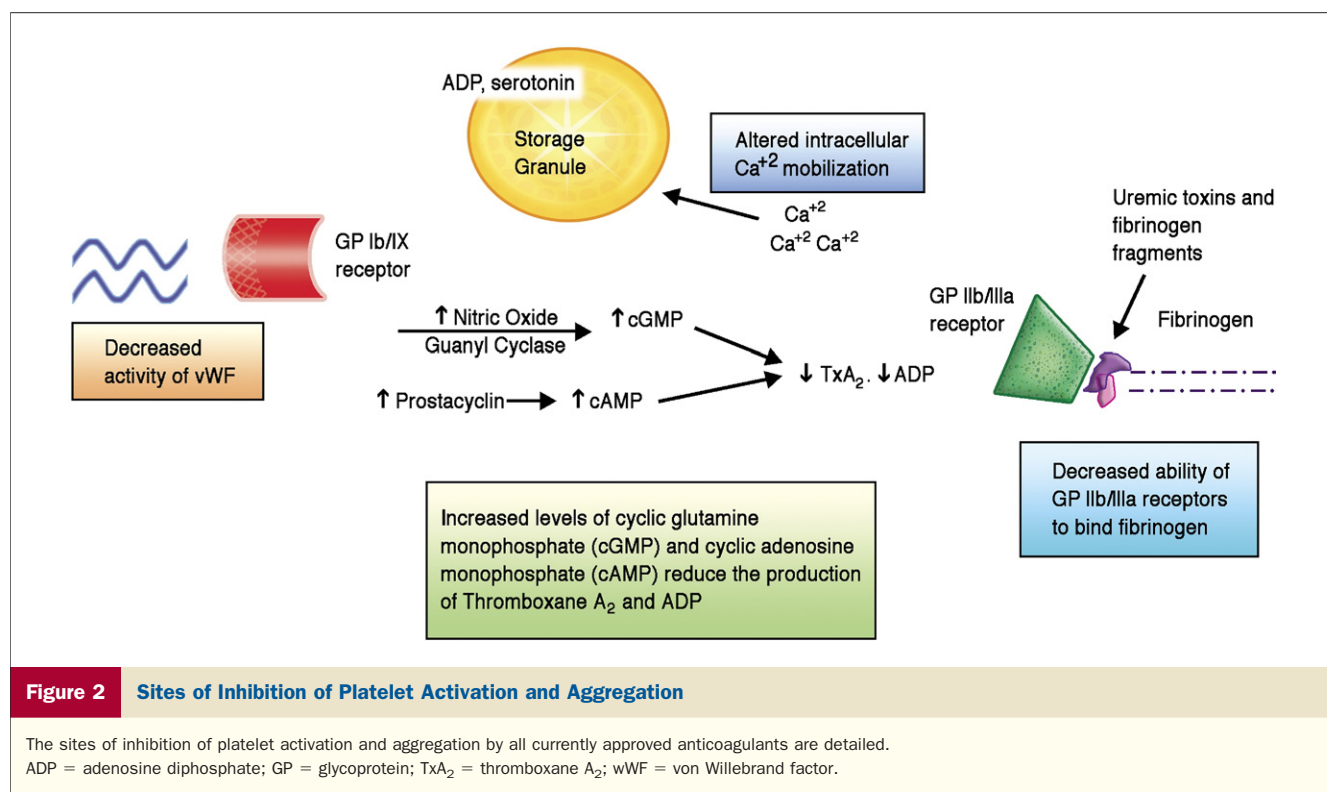


Table 2 Antiplatelet and Antithrombotic Agents, Recommended Doses, Routes of Elimination, Effect of Renal Failure on Dose, and Potential Strategies to Reverse Their Effect

Drug	Recommended Dose	Route of Elimination	Half-Life	Effect of Renal Failure on Dose	Strategy for Reversal in Patients With Bleeding
Aspirin	81–325 mg	Renal (pH-dependent)	2–19 h	None	Discontinue; platelet transfusion, and desmopressin
Clopidogrel and active metabolite	Loading dose: 300–600 mg Maintenance dose: 75 mg	Renal (50%), feces (50%)	6 h	None	Discontinue; platelet transfusions and desmopressin
Prasugrel	Loading dose: 60 mg Maintenance dose: 10 mg	Renal (60–70%)	2–15 h	None	Discontinue; platelet transfusions and desmopressin
Ticagrelor	Loading dose: 180 mg Maintenance dose: 90 mg PO BID	Biliary	6–13 h	None	Discontinue
Abciximab	250 $\mu\text{g}/\text{kg}$ bolus followed by 0.125 $\mu\text{g}/\text{kg}/\text{min}$ for 12 h	Spleen, RES	30 min	None	Discontinue; platelet transfusions and desmopressin
Tirofiban	0.4 $\mu\text{g}/\text{kg}/\text{min}$ 30-min bolus followed by 0.1 $\mu\text{g}/\text{kg}/\text{min}$	Renal (40%–70%)	1.4–1.8 h	$\text{CrCl} < 30 \text{ ml/min/1.73 m}^2$: 0.2 $\mu\text{g}/\text{kg}/\text{min}$ 30-min bolus followed by 0.05 $\mu\text{g}/\text{kg}/\text{min}$	Discontinue; FFP
Eptifibatide	180 $\mu\text{g}/\text{kg}$ bolus followed by 2.0 $\mu\text{g}/\text{kg}/\text{min}$ for 72 h	Renal (50%)	25 min	$\text{CrCl} < 50 \text{ ml/min/1.73 m}^2$: 180 $\mu\text{g}/\text{kg}$ bolus followed by 1 $\mu\text{g}/\text{kg}/\text{min}$ for 72 h; contraindicated in patients on hemodialysis	Discontinue; FFP
Unfractionated heparin	PTT: 50–70 s	RES	1–1.5 h	None	Protamine
Enoxaparin	1 mg/kg SC every 12 h	Renal (40%)	4–7 h	Decrease to 1 mg/kg SC daily	Partial reversibility (2/3) to protamine
Fondaparinux	2.5 mg SC daily	Renal	17–21 h Increases in renal failure	Avoid if $\text{CrCl} < 30 \text{ ml/min/1.73 m}^2$	Recombinant factor VIIa (90 $\mu\text{g}/\text{kg}$) Based on laboratory data only
Bivalirudin	0.75 mg/kg IV bolus followed by 1.75 mg/kg/h during procedure	Renal	25 min Increases if $\text{CrCl} > 30 \text{ ml/min/1.73 m}^2$	Avoid if $\text{CrCl} < 30 \text{ ml/min/1.73 m}^2$	No single antidote; may consider hemodialysis

BID = twice a day; CrCl = creatinine clearance; FFP = fresh frozen plasma; IV = intravenous; PO = orally; PTT = partial thromboplastin time; RES = reticuloendothelial system; SC = subcutaneously.

Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Registry found that bleeding risk is higher in patients administered excess doses of GPIs (OR: 1.36; 95% CI: 1.10 to 1.68), and it is further increased in patients with renal insufficiency (OR 4.12; 95% CI: 2.65 to 5.75). These data further underscore the importance of calculating the CrCl before administering GPIs (45).

Heparin. Unfractionated heparin reduces early ischemic events in patients with ACS with and without CKD (45–48). The half-life of enoxaparin in dialysis patients is twice as long as in healthy volunteers. The total clearance of enoxaparin is 1.9 times lower and its half-life 1.7 times longer in patients with renal insufficiency (49–57). A retrospective study evaluated the outcomes of bleeding and death in patients with CKD administered enoxaparin demonstrated an increase in total bleeding, major bleeding as well as deaths (58). A recent substudy of the EXTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment)–TIMI 25 trial showed that with every 30 ml/min decrease in CrCl, the risk of major and minor bleeding increased by 50% (59).

Fondaparinux. Fondaparinux is a synthetic heparin analogue that causes an irreversible conformational change in antithrombin. Fondaparinux is given a class I ACC/AHA

recommendation in ACS patients with high bleeding risk. In the OASIS-5 (Fifth Organization to Assess Strategies in Acute Coronary Syndrome) trial (59), the composite end-point was lower with fondaparinux compared to enoxaparin and reached significance only in patients with GFR $< 58 \text{ ml/min/1.73 m}^2$. The rates of bleeding were lower across all quartiles of renal dysfunction.

Bivalirudin. Bivalirudin is a synthetic direct thrombin inhibitor with a half-life of 25 min and significant renal clearance (62–64). In a substudy of the ACUTY (Acute Catheterization and Urgent Intervention Triage Strategy) trial (62) in CKD patients, there were fewer bleeding complications with bivalirudin than with unfractionated heparin plus GPI (65). However, as bivalirudin is renally cleared, patients with $\text{CrCl} < 30 \text{ ml/min}$ should not receive bivalirudin as most of these patients were excluded from the ACUTY trial.

Direct factor Xa inhibitors. Currently, a number of direct factor Xa inhibitors are being evaluated in clinical trials in patients with ACS (66,67). Dabigatran (68–71) is a recently approved Xa inhibitor in patients with nonvalvular atrial fibrillation. The half-life of dabigatran increases with renal dysfunction, and its use is contraindicated in patients with $\text{CrCl} < 30 \text{ ml/min/1.73 m}^2$ (69). Data on the safety and efficacy of these agents for treating CKD are lacking.

Table 3 Safety and Efficacy of Antiplatelet and Antithrombotic Agents Stratified by Category of CKD								
Drug	CKD 1	CKD 2	CKD 3	CKD 4	CKD 5	Comments	RCT/RP/SC/R/MA/SA	Evidence
Aspirin	S, E	S, E	S, E	S, E	S, E		RCT (12,16,17), RP (13), R (14), MA (18)	Sufficient
Clopidogrel	S, E	S, E	US, NE	US, NE	US, NE	Increased risk of minor bleeding and risk of blood transfusions in CKD 3–5. Lack of efficacy in CREDO (20) and CURE (22) trials in CKD 3–5. Further studies needed to establish efficacy of standard dose vs. double dose clopidogrel in patients with CKD	RCT (23), SA (20,22)	Further studies of CKD 3–5 patients needed
Prasugrel	S, E	S, E	UK	UK	UK	No studies currently available on safety and efficacy in patients with CKD. No difference based on pharmacokinetic and pharmacodynamic data.	RCT (29)	Further studies of CKD patients needed
Ticagrelor	S, E	S, E	S, E	S, E	S, E	May be considered over standard dose clopidogrel. Further trials needed to assess efficacy vs. double dose clopidogrel.	RCT (33), SA (34)	Sufficient
Abciximab	S, E	S, E	S, E	S, E	S, E	No interaction observed between abciximab, worsening renal function and ischemic/bleeding outcomes.	SA (40), SC (37), R (36)	Sufficient
Tirofiban	S, E	S, E	S, E	S, E	S, E	No interaction observed between tirofiban, worsening renal function, and ischemic/bleeding outcomes. Dose needs to be adjusted for CrCl <30 ml/min/1.73 m ²	SC (38), SA (39,40)	Sufficient
Eptifibatide	S, E	S, E	S, E	S, E	S, E	No interaction observed between eptifibatide, worsening renal function, and ischemic/bleeding outcomes. Dose needs to be adjusted for CrCl <50 ml/min/1.73 m ²	SA (43)	Sufficient
Unfractionated heparin	S, E	S, E	S, E	S, E	S, E	May be preferred over LMWH in CKD 4–5	RCT (47)	Sufficient
LMWH	S, E	S, E	S, E	US, E	US, E	Increased risk of major and minor bleeding in CKD 4–5. Dose should be reduced by half in patients with CrCl <30 ml/min/1.73 m ² . UFH may be preferred over LMWH in this group.	SA (59), RP (58)	Sufficient
Fondaparinux	S, E	S, E	S, E	A	A	May be preferred over LMWH in patients with GFR between 30 and 58 ml/min/1.73 m ² . Avoid using if CrCl <30 ml/min/1.73 m ² .	RCT (61), SA (62)	Sufficient
Bivalirudin	S, E	S, E	S, E	A	A	Superior to heparin plus GPI in patients undergoing PCI, and is associated with fewer ischemic and bleeding complications. Avoid using if CrCl <30 ml/min/1.73 m ² .	RCT (63,64), SA (65)	Sufficient
Direct factor Xa inhibitors	UK	UK	UK	UK	UK	No studies on safety and efficacy of these agents in patients with CKD currently available.		Further studies of CKD patients needed

A = avoid; E = effective; GPI = glycoprotein inhibitor; LMWH = low molecular weight heparin; MA = meta-analysis; NE = nonefficacious; PCI = percutaneous coronary intervention; R = registry; RCT = randomized clinical trial; RP = retrospective; S = safe; SA = subanalysis; SC = single center; UFH = unfractionated heparin; UK = unknown; US = unsafe; other abbreviations as in Tables 1 and 2.

Conclusions

There is a clear dearth of studies evaluating the safety and efficacy of these drugs for treating CKD patients, and most of the recommendations are based on single-center data or post-hoc analyses. Novel therapies may help overcome some of the complications observed in these patients, but further randomized trials are warranted to objectively evaluate their efficacy for this increasingly common subgroup of patients.

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Key Words: acute coronary syndrome(s) ■ antiplatelet ■ antithrombotic ■ bleeding ■ chronic kidney disease ■ non-ST-segment elevation myocardial infarction ■ ST-segment elevation myocardial infarction ■ unstable angina.